1014-62 **Comparison of Novel Strategy Therapies for Obstructive Hypertrophic Cardiomyopathy: Relation of Relief of Left Ventricular Outflow Obstruction to Improved Symptoms and Health-Related Quality of Life Parameters**

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Background: Left ventricular (LV) outflow obstruction is present in about a third of patients with hypertrophic cardiomyopathy (HCM), and may cause disabling symptoms. Alcohol septal ablation (ASA) and dual chamber (DDD) pacing have been proposed as alternative therapies to cardiac surgery for relief of LV outflow obstruction. Methods: We compared the impact of ASA and DDD on LV gradient, symptoms and health-related quality of life (HRQL) in a randomized propective study involving 70 patients with obstructive HCM and drug-refractory symptoms. The demographic and clinical characteristics of the 2 arms were similar. Patients completed the SF-36 Health Survey and a symptom measure at baseline (prior to randomization), 3 and 6 months. Results: Both procedures significantly reduced the LV outflow gradients determined at cardiac catheterization: ASA arm, the mean (SD)gradient reduced from 105 (32) mm Hg to 33 (32) mm Hg [a change of 72 (37) mm Hg, or 69%; and DDD arm, from 101 (36) mmHg to 49 (39) mm Hg (a change of 51 (32) mm Hg, or 50%]. ASA resulted in significantly (about 20 mm Hg) greater reduction in LV gradient, p=0.017. Of the 70 patients randomized, 32 DDD and 29 ASA were available for HRQL analysis. Both therapies resulted in significant and equal improvement in all symptom and HRQL outcomes from baseline to 3 months, with no further change at 6-month follow-up. There was no significant correlation between changes in symptoms or HRQL and reductions in LV gradients, perhaps due to the dynamic nature of the LV outflow obstruction. Conclusions: (1) ASA and DDD are both effective in relieving LV obstruction in most patients; and 2) both DDD and ASA are associated with significant symptom and HRQL benefits at 3 months that persist to 6 months. As the symptomatic and HRQL benefits were equivalent, DDD pacing should perhaps be tried first. ASA may then be performed in patients with residual obstruction and symptoms without concerns about inducing heart block.

1014-63 **Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy: An Analysis of the Patients With Dissatisfactory Intervention Results**

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Background: In 90% of the patients (pts). with symptomatic hypertrophic obstructive cardiomyopathy (HOCM) the outflow gradient (LVOTG) can significantly be reduced or removed by septal ablation (PTSMA). Pts. with a dissatisfactory LVOTG response are not yet characterized sufficiently.
Results: From 279 pts. re-evaluated 3 months after PTSMA, 36 (13%) had PTSMA failure (PF) defined as a less than 50% LVOTG reduction. On average, these pts. were younger (50±18 vs. 54±14 years; p<0.01), had a thicker septum (22±4 vs. 20±4 mm; p<0.05), a higher baseline LVOTG (69±33 vs. 58±33 mm Hg; p<0.01), and a lower CK release after PTSMA (477±228 vs. 556±272U/l; p<0.05).
The main cause for PF was an insufficient PTSMA lesion on 2D-echo at follow-up (n=22; successful re-PTSMA in 6 pts., surgery in 1 pt. and spontaneous LVOTG reduction in 8 pts. within the following 12 months). Suboptimal scar localization, observed in 7 pts. treated before routine echocardiographic guidance (MCE) for PTSMA and requiring a re-PTSMA in 4 pts. and surgery in 2 pt., was not seen with MCE-guidance any more.
Another group of pts. with PF showed persisting SAM and LVOTG despite a sufficient PTSMA scar due to excessive elongation of the mitral leaflets (n=5; spontaneous LVOTG elimination in one of them within 12 months). One pt. each had coexistent fibromuscular subaortic stenosis and severe midcavity obstruction which both did not respond to PTSMA.
Conclusions: Even with MCE guiding, younger pts. with a thicker septum, and those with markedly elongated mitral leaflets seem to be less suitable for PTSMA. Furthermore, LVOTG elimination may need up to 1 year. Pre-interventional pt. selection, echocardiographic assessment, and pt. information should take these findings into consideration.

1014-64 **Prevalence and Spectrum of Thin Filament Mutations in Patients With Hypertrophic Cardiomyopathy: A Comprehensive Mutational Analysis of Troponin T, Troponin I, Alpha Tropomyosin, and Cardiac Actin**

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Background: Thin filament mutations are reported to cause ~20% of Hypertrophic Cardiomyopathy (HCM) and display a diverse phenotype. However, the frequency of these mutations and their associated phenotype in a single large cohort have not been reported. We determined the prevalence and spectrum of mutations in the genes encoding the thin filament proteins cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), alpha tropomyosin (*TPM1*), and cardiac actin (*ACTC*) in a large cohort of unrelated HCM patients, and searched for defining clinical characteristics for thin filament-HCM.
Methods: DNA from 395 unrelated patients with HCM was obtained and analyzed. Mutational analysis of all protein coding exons of *TNNT2* (15 exons), *TNNI3* (8), *TPM1* (9), and *ACTC* (6) was performed using polymerase chain reaction, denaturing high performance liquid chromatography, and DNA sequencing. The clinical data were maintained in a database independent of the patient genotype.
Results: Overall, only 19 patients (4.8%) were identified having 12 distinct thin filament mutations: 9 with *TNNT2* mutations, 6 with *TNNI3* mutations, 3 with *TPM1* mutations, and 1 with an *ACTC* mutation. Of the 12 unique missense mutations identified, 8 (67%) were novel mutations. As a group, patients with thin filament mutations were not significantly different from the rest of the cohort in age at diagnosis, left ventricular wall thickness (LVWT), gradient, or family history of HCM or sudden death. However, when compared to patients with beta myosin heavy chain mutations (n=54), patients with thin filament mutations had less hypertrophy (LVWT = 19.8 ± 6 mm versus 24.3 ± 8 mm, $p = 0.04$).
Conclusions: This study represents a comprehensive evaluation for mutations in the genes encoding the thin filament of the cardiac sarcomere at a large, tertiary referral center for HCM. Here, thin filament mutations were identified in <5% of the HCM cohort. Moreover, except for a lesser degree of hypertrophy when compared to patients with thick filament HCM on the basis of mutations in the beta myosin heavy chain, there were no clinical features to distinguish this small subset of thin filament-HCM from HCM due to mutations in other genes.

1014-65 **Evidence That Left Ventricular Outflow Tract Obstruction Is a Predictor of Outcome in Patients With Hypertrophic Cardiomyopathy**

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Background. One of the most visible and quantifiable features of hypertrophic cardiomyopathy (HCM) has been the left ventricular (LV) outflow tract gradient. Major therapeutic interventions (such as surgery, alcohol septal ablation and pacing) have been introduced to relieve subaortic obstruction and disabling symptoms. However, the significance of LV outflow obstruction with regard to clinical outcome in HCM has been the subject of controversey and remains incompletely unresolved.
Methods. We assessed the impact of LV outflow gradient on mortality and morbidity in a large HCM cohort prospectively followed over 6.3±6.2 years.
Results. Of 1101 consecutive patients, 127 (12%) died of HCM and 196 (18%) developed severe progressive heart failure-related symptoms (NYHA functional classes III/IV); at initial evaluation, 273 study patients (25%) had LV outflow obstruction under basal conditions with continuous wave Doppler (gradient, ≥30mm Hg). Probability of HCM-related mortality and progression to severe disabling symptoms was significantly greater in patients with outflow obstruction than in those without (OR 2.0 and 4.4, respectively; p<0.0001 for both end-points), and was most substantial in obstructive patients ≥ 40 years old (p<0.001). HCM mortality and morbidity due to obstruction did not increase with greater magnitude of gradient above the threshold of 30mm Hg. Multivariate analysis showed outflow obstruction to be a strong and independent predictor of HCM-mortality and severe symptoms (OR 1.6; p=0.018) among several other disease variables. Likelihood of sudden death was also greater in patients with obstruction (OR 1.9; p=0.014), although the positive predictive value for obstruction was low (i.e., only 7%).
Conclusions. Basal LV outflow obstruction (gradient, ≥30mm Hg) is a strong and independent predictor of progression to severe symptoms and cardiovascular mortality in HCM. Therefore, treatment interventions that reduce outflow gradients can be expected to favorably influence quality of life and long-term prognosis in severely symptomatic patients with obstructive HCM, and could possibly be justified somewhat earlier at lesser gradients than is current practice.

1014-66 **Left Atrial Volumetric Remodeling Predicts Functional Capacity in Hypertrophic Cardiomyopathy**

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Background: Left atrial volumetric remodeling (LAR) is a marker of hypertensive left ventricular (LV) hypertrophy and associated cardiovascular events and probably represents chronic hemodynamic overload. Its role as an indicator of disease severity in primary hypertrophic cardiomyopathy (HCM) has not been reported. We, therefore, compared the association of two-dimensional echocardiographically-determined LAR and other structural and hemodynamic parameters with objective measures of exercise functional capacity in 26 patients (14 males, 12 females, mean age=37 years).
Methods: BSA-normalized left atrial volume by modified Simpson's biplane method, M-mode (MM) and trans-mitral Doppler (E/A ratio) echocardiographic measures were obtained in patents undergoing cardiac catheterization within 24 hours of echocardiographic assessment and correlated with metabolic treadmill stress testing performed during the same admission. Magnetic resonance imaging (MRI)-determined LV mass was also obtained in a subset of 13 subjects.
Conclusions: Volumetric LAR in HCM patients correlated significantly and consistently with metabolic stress testing parameters. LAR predicted objective functional capacity at least as well as resting invasive hemodynamic assessment and was superior to other forms of echocardiographic and MRI LV mass assessment.

Spearman Univariate Correlation Coefficients

All results are non-significant except as indicated * p<0.05 ** p<0.01 *** P<0.001	Maximum VO2 Normalized for Body Mass	Anaerobic Threshold	Treadmill Exercise Time
LA Volume-Normalized	-0.50**	-0.60***	-0.45**
Diastolic Septal Thickness (MM)	-0.04	0.03	0.08
Septal/Posterior Wall Ratio (MM)	-0.08	-0.11	-0.16
E/A Ratio (Doppler)	0.17	0.34*	0.19
Left Ventricular Mass (MRI)	0.12	0.11	-0.37
Pulmonary Artery Systolic Pressure	-0.50**	-0.27	-0.19
Pulmonary Capillary Wedge Pressure	-0.50**	-0.35*	-0.24
LV End-Diastolic Pressure	-0.30	-0.08	-0.04

1014-67 Long-Term Outcome in Patients With Latent (Provocable) Obstructive Hypertrophic Cardiomyopathy

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BACKGROUND: Subaortic obstruction in hypertrophic cardiomyopathy (HCM) may be classified as obstruction at rest or latent (LO). There is only limited information on long-term clinical outcome in HCM patients (pts) presenting with LO.
METHODS: A retrospective study of 127 pts (73% male) with LOHCM was performed. Inclusion criteria were: unexplained left ventricular hypertrophy with no outflow gradient (LVOTGR) at rest and >30 mmHg after provocation, documented by echo (n = 72) or catheterization (n = 55). Symptoms, clinical findings, mortality and cardiovascular morbidity were analyzed.
RESULTS: The mean age at diagnosis was 45.1 ± 15.8 years. At baseline the mean LVOTGR at rest was 7±8 mmHg and 64±26 mmHg after provocation. The mean septal thickness was 18.5±3.9 mm, with hypertrophy limited to the basal 1/3 of septum in 74 pts (58%), and to the proximal 2/3 in 37 pts (29%). The mean left atrial diameter was 40±6 mm. Most common symptoms were dyspnea (33%), chest pain (28%) and pre-/syncope (15%). During a follow-up of 12.8±8.3 years from diagnosis cardiovascular mortality was 5.5% (7/127) and annual cardiovascular mortality 0.4%, due to sudden cardiac death (SCD) (n=4), CHF (n=2) and stroke (n=1). SCD pts had more extensive septal hypertrophy. At 15 years of follow-up survival for LOHCM of 88±4% was not different from that for the age- and gender-matched population. Morbid events occurred in 59 pts (46%), the most frequent being atrial fibrillation (28%), cerebrovascular events (12%), myocardial infarction (9%) and CHF (9%). At the last follow-up pts were on beta-blockers (78%), disopyramide (19%) or/and calcium channel blockers (19%). Surgical or chemical myectomy was performed in 14 pts (11%). Seven pts received AICD, for secondary prevention (1) and primary prevention (6). Only left atrial enlargement at baseline and older age at diagnosis were independent predictors of cardiovascular morbidity.
CONCLUSION: The majority of pts with LOHCM have less extensive hypertrophy and a more favorable prognosis than other types of HCM. However, in the presence of extensive hypertrophy, left atrial enlargement and older age at diagnosis, LO does have significant cardiovascular morbidity and mortality.

1014-82 Relation Between Angiotensin-Converting Enzyme II Genotype and Cardiovascular Events in Patients With Hypertrophic Cardiomyopathy

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Background: The renin-angiotensin system plays a part in the pathophysiology of cardiovascular disease. Many studies showed the benefits of angiotensin converting enzyme (ACE) inhibitors in congestive heart failure. However, ACE inhibition in patients with hypertrophic cardiomyopathy (HCM) was reported to aggravate hemodynamics and lead to hypotension and excessive systolic emptying. The insertion/deletion (I/D) polymorphism of the ACE gene is a marker linked to differences in plasma and cardiac ACE activity and an independent risk factor for several heart diseases. Therefore, the purpose of this study was to examine the relation between the ACE genotypes and the occurrence of cardiovascular events in patients with HCM. Methods and Results: We genotyped the I/D polymorphism of the ACE gene in genetically independent 151 patients with HCM. The cardiovascular events were defined as sudden cardiac death, congestive heart failure, thromboembolism, stroke, syncope, atrial fibrillation and sustained ventricular tachycardia. Patients with one or more history of the cardiovascular events were 65 (43%), and patients without history of the cardiovascular events were 86 (57%). Distribution of the ACE genotypes (DD, ID, and II) among the total patients with HCM was 14%, 46%, and 40%, respectively. The cardiovascular events were documented in 36% with DD, 32% with ID, and 58% with II. Allele frequency for the I allele was 0.71 in the group with the cardiovascular events and 0.56 in the other group. There was a significant difference in genotypes between the two groups by chi-square test (P<0.01). The odds of the cardiovascular events was 3.1-fold higher in patients with the II genotype than in the other genotypes. Conclusion: These findings suggest that the II genotype of the ACE gene is a significant risk factor for the cardiovascular events in patients with HCM.

1014-83 Reduction in Mitral Regurgitation After Alcohol Septal Ablation in Patients With Hypertrophic Obstructive Cardiomyopathy

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Background: Mitral Regurgitation (MR) is a common finding in patients with hypertrophic obstructive cardiomyopathy (HOCM). This is thought to be related to systolic anterior motion of the mitral valve. Improvements in MR have been documented in parallel with reduction in left ventricular outflow tract (LVOT) gradient with both dual chamber pacing and with surgical myectomy. In this study, we examined reduction in MR and associated changes in LVOT gradient and treadmill exercise time before and after alcohol septal ablation. **Methods:** We reviewed transthoracic echocardiograms from 40 patients who underwent alcohol septal ablations performed at our institution. Echocardiograms were done before the procedure and in follow-up 3 months after the procedure. In addition to measuring LVOT gradient and treadmill exercise time, we assessed degree of MR by measuring the area of color flow regurgitant jet, ratio of color flow regurgitant jet area to left atrial area, and the peak mitral inflow E velocity.
Results: At baseline, 39 of 40 patients had MR as measured by color flow doppler. There was a significant reduction in MR measured by transthoracic echocardiography at 3 months follow-up. The pre-procedure mean mitral regurgitant jet area was 5.0 cm^2. This decreased to 2.1 cm^2 at 3 months follow-up (p<0.001). The pre-procedure mean mitral regurgitant jet area/ left atrial area was 0.38. This decreased to 0.20 at 3 months follow-up (p<0.001). The pre-procedure mean peak mitral inflow E velocity was 0.87 m/s. This decreased to 0.79 m/s at 3 months follow-up (p<0.05). The pre-procedure mean LVOT gradient was 85.6 mm Hg. This decreased to 26.3 mm Hg at 3 months follow-up (p<0.001). The pre-procedure mean treadmill exercise time was 233.1 seconds. This increased to 361.8 seconds at 3 months follow-up (p<0.001). **Conclusions:** Alcohol septal ablation results in improved LVOT gradient and treadmill exercise time in patients with HOCM. This is associated with a significant reduction in MR. The reduction in MR may be an independent contributing factor to the improvement in exercise time and symptoms noted in these patients.

1014-84 Noninvasive Assessment of Coronary Flow Velocity Reserve Impairment in Patients With Hypertrophic Cardiomyopathy

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Background.Microvascular impairment occurs frequently in hypertrophic cardiomyopathy patients (HCM), often without evidence of coronary artery stenosis but with impairment of coronary flow velocity reserve (CFVR). We tested the hypothesis that CFVR, noninvasive monitored, can be impaired in HCM and could be related to the severity of cardiac hypertrophy.
Methods. We studied 18 HCM (13 males and 5 females), mean age 51 years (range 16±72 years) and 21 control group patients. We evaluated CFVR in the left anterior descending coronary artery (LAD) with contrast enhanced transthoracic Doppler (CE-TTE) during adenosine infusion. The pulsed wave Doppler of blood flow velocity was recorded in the LAD at rest and after maximum vasodilation by adenosine infusion (140[mu]g/Kg/min in 5 minutes).
Results. In HCM, CFVR was impaired compared to control group (2.3±0.88 Versus 3.29±0.53 , p<0.001). A significantly, greater percentage of HCM had severe reduction of CFVR (<2.0) compared to control group (8/18, 44% Versus 0/21, 0%, p=0.001). Diastolic mean velocity at rest was significantly higher in HCM with reduced CFVR compared both to control group (56.5±18.5 Versus 32.8±15.5 cm/sec, p<0.01) and to HCM with normal CFVR (56.5±18.5 Versus 31.9±6.5 cm/sec, p<0.01). However, diastolic mean velocity during hyperemia was not statistically different between the 2 groups (92±28 Versus 102±30 cm/sec, p=ns) but in HCM with reduced CFVR it was statistically lower when compared to both control group (76.2±22.5 Versus 102±30.4 cm/sec, p<0.05) and HCM with normal CFR (76.2±22.5 Versus 104.5±30.4, p<0.05).Furthermore, HCM with greater cardiac hypertrophy (>20 mm) had CFVR severely reduced in comparison to HCM with less degree of myocardial involvement (2.0±0.8 Versus 2.8±0.8, p<0.05).
Conclusion. This study demonstrated that in HCM, CFVR is significantly impaired because of increased baseline resting diastolic mean velocity resulting in a reduced vasodilatatory capacity and CFVR impairment is related to the degree of cardiac hypertrophy. Noninvasive CEE-TTE assessment of CFVR, could be a simple and reliable method in detecting and monitoring microcirculatory dysfunction in HCM.

1014-85 Injury Size and Location Induced by Percutaneous Transluminal Septal Myocardial Ablation in Hypertrophic Obstructive Cardiomyopathy: Effect on Gradient Reduction

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Background: Percutaneous transluminal septal myocardial ablation (PTSMA) reduces left ventricular outflow tract (LVOT) obstruction in patients with symptomatic hypertrophic obstructive cardiomyopathy (HOCM). The purpose of the study was to evaluate by contrast-enhanced magnetic resonance imaging (MRI) the effect of myocardial injury size and location induced by PTSMA on LVOT gradient reduction.
Methods: Twenty-four patients (age 52± 15 years) underwent contrast-enhanced (gadolinium-DTPA) MRI 1 month after PTSMA for assessment of PTSMA induced myocardial injury size. Location of hyperenhanced myocardium was compared with ethanol infused target septal branch, site of balloon inflation and the volume of alcohol administered.